FEE

DP BARCODE: D373465; **FILE SYMBOL No.**: 35935-53; **PRODUCT**: Fluroxypyr Technical

Date: March 17, 2010

SUBJECT: Product Chemistry Review of Fluroxypyr Technical TGAI / MUP

FROM: Shyam B. Mathur, PhD
Product Chemistry Team Leader
Technical Review Branch/RD (7505P)

3/18/10

TO: Michael Walsh / Kathryn Montague, RM 23
Herbicide Branch / RD (7505P)

DP BARCODE: D373465
DECISION No.: 425345
File Symbol No.: 35935-53
PRODUCT: Fluroxypyr technical TGAI I / MUP
PCC: 128968
REGISTRANT: Nufarm Ltd.
USE: Herbicide
FOOD USE: Yes

INTRODUCTION:

The registrant Nufarm Ltd. has submitted an application to add another source to the existing registration for the Fluroxypyr technical. The fluroxypyr TGAI/MUP is produced by [redacted]. The registrant has submitted an alternate CSF (dated 11-20-09) reflecting the additional production site. The basic CSF (dated 03-23-09) represents the production by [redacted]. In support of the application, the registrant has submitted 830 series group A data with MRID No. 479401-01. No group B product chemistry data was submitted. TRB has been asked to evaluate the product chemistry data submitted and determine acceptability of the proposed alternate CSF.

SUMMARY OF FINDINGS:

1. The registrant has submitted a CSF for alternate formulation (dated 11-20-09) for fluroxypyr TGAI/MUP. The average purity of the active ingredient in TGAI/MUP is 97.0%, as determined by the five batch analysis. The proposed certified limits for the AI are based on the standard certified limits as set forth in 40CFR§158.350(b)(2). The proposed limits for impurities ≥ 0.1% are based on the preliminary analysis and expected to occur in normal commercial production. The product chemistry data submitted corresponding to guideline reference 830.1550 (product identity & composition) and 830.1750 (certified limits) satisfy the data requirements of 40CFR§158.320 and 158.350 respectively [MRID No. 479401-01].

2. The product chemistry data submitted corresponding to guideline reference 830.1600 (description of material used to produce the product) satisfy the data requirements of 40CFR§ 158.325 [MRID No. 479401-01].

Manufacturing process information may be entitled to confidential treatment

Product ingredient source information may be entitled to confidential treatment

3. The product chemistry data submitted corresponding to guideline reference 830.1620 (description of production process) satisfy the data requirements for 40CFR§158.330. The manufacturing process for fluroxypyr TGAI/MUP consists of [redacted]. The applicant has provided the details of the chemical process with reaction conditions, equipment used, working up procedures, and quality assurance steps [MRID No. 479401-01].

4. The product chemistry data submitted corresponding to guideline reference 830.1670 (discussion on the formation of impurities) satisfy the data requirements for 40CFR§158.340. During the production of fluroxypyr TGAI/MUP, the registrant discussed the formation of [redacted] major impurity present at the concentration of >0.1%. During the preliminary analysis [redacted] other [redacted] impurities were identified in concentrations of ≤ 0.1% and therefore are not listed in the CSF. [redacted] and [redacted] are other [redacted] impurities present in the fluoxypyr TGAI/MUP. The registrant has stated that there is no possibility of the formation of impurities of toxicological concern as there are no preexisting conditions or starting materials present in the production process which are required for their formation [MRID No. 479401-01].

5. The data submitted corresponding the guideline reference 830.1700 (preliminary analysis) does not satisfy the data requirements of 40CFR§158.345. The study was conducted under GLP requirements in compliance with 40CFR§160. The analysis study was performed by G. C. Laboratories Ltd., Stotfold, Hitchin, England. Five representative batches of the fluroxypyr TGAI/MUP (produced by [redacted]) were analyzed for percent active ingredient and the impurities. The active ingredient and the [redacted] impurities were identified and quantified by using HPLC-UV with external standard quantification method. Few of the impurities were identified by using GC-FID method. [redacted] No details of the experimental procedures have been provided [MRID No. 479401-01].

6. The data submitted corresponding the guideline reference 830.1800 (enforcement analytical method) satisfy the data requirements of 40CFR§158.355. The purity of the AI in the TGAI/MUP was determined by HPLC-UV by internal standard method. The analytical method utilized an Agilent Zorbax RX-C8 column, 250 x 4.6 mm with UV detector operating at 238 nm. The method was validated for precision, accuracy and linearity [MRID No. 479401-01].

7. No data was submitted corresponding to 830 series group B product chemistry (physical-chemical properties) data.

CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for fluroxypyr technical TGAI/MUP (produced by [redacted]) and has concluded that:

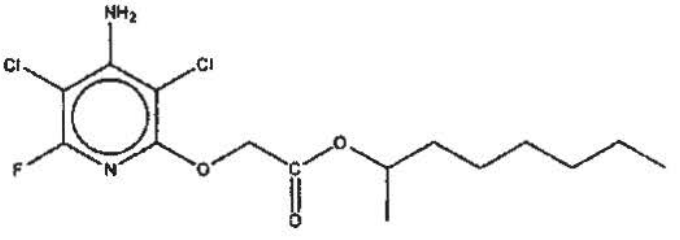
1. All the product chemistry data submitted corresponding to the guidelines 830 Series group A are acceptable; except for the guideline 830.1700 (five batch analysis).

2. The registrant must provide the details of the experimental procedures for the analytical methods used for the identification and quantification of the active ingredient (fluroxypyr) and the associated impurities.

3. The proposed CSF for alternate formulation (dated 11-20-09) is not acceptable until the additional data on the details of the experimental procedures for the analytical methods are received and reviewed.

830.1550. Product identity & Composition: (MRID No. 475407-01)

Active Ingredient Identity:

CAS No.:	81406-37-3
Common name/alias:	Fluroxypyr-meptyl
Chemical Names:	
IUPAC:	(*RS*)-1-methylheptyl 4-amino-3,5-dichloro-6-fluoro-2-pyridyloxyacetate
CAS:	1-methylheptyl [(4-amino-3,5-dichloro-6-fluoro-2-pyridinyl)oxy]acetate
Molecular formula:	$C_{15}H_{21}Cl_2FN_2O_3$
Molecular weight:	367.24
Structure:	

Manufacturing process information may be entitled to confidential treatment
Product ingredient source information may be entitled to confidential treatment

DP BARCODE: D373465; **FILE SYMBOL No.:** 35935-53; **PRODUCT:** Fluroxypyr Technical

Table 1. Manufacturing and Impurity Data for fluroxypyr technical TGAI / MUP

GLN	Requirement	MRID	Status	Details and /or Deficiency
830.1550	Product Identity and composition	Basic CSF (11-20-09)	U	The NC of AI (97.0%) is supported by 5 batch analysis & agrees with the label claim nominal concentration. [redacted] impurities are listed on the CSF.
8301600	Description of materials used to produce the product	479401-01	A	The description & composition for all the starting materials used to produce the fluroxypyr technical ([redacted]) have been provided by the registrant
830.1620	Description of production process	479401-01	A	The AI was produced [redacted]. The production process has been described in full details.
830.1670	Discussion of formation of impurities	479401-01	A	The registrant has provided the complete mechanisms of formation, quantification and identification of all the impurities present at the levels of ≥ 0.1%.
830.1700	Preliminary analysis	479401-01	U	Five representative batches fluroxypyr technical (produced by [redacted]) were analyzed for percent active ingredient and the impurities. The HPLC-UV in combination of GC-FID methods were used for the identification of the AI and the impurities. The five batch analysis supported the proposed CSF for alternate formulation.
830.1750	Certified limits	479401-01	A	The proposed certified limits for the AI are based on standard certified limit table, whereas, those of impurities are based on five batch analysis.
830.1800	Enforcement analytical method	479401-01	A	The HPLC-UV (238 nm) with internal standard method was used for the determination of the AI content in the TGAI/MUP. The method was validated for precision, linearity and accuracy..

A = Acceptable; N = unacceptable (see Deficiency); N/A = Not Applicable; G = Data gap; I = In progress or need upgrade; U = Up-grade (additional information required

830.1800. Enforcement of analytical method: (MRID No. 479401-01)

Determination of AI by HPLC-UV method with internal standard method

The five batches of NUP-09005 were assayed by a validated analytical method based on high performance liquid chromatography (HPLC) employing an internal standard technique using ultraviolet (UV) detection.

The following conditions were used.

Instrument:	Varian 9012 solvent delivery system Applied Biosystems 759A absorbance detector HP Series 1050 autosampler
Column:	Agilent Zorbax RX-C8 (250 x 4.6 mm)
Column temperature:	30 °C
Mobile phase	A = water plus 0.2% perchloric acid B = acetonitrile C = methanol

Time (min)	%A	%B	%C
0	65	5	30
40	25	5	70
50	25	5	70
51	65	5	30
56	65	5	30

Flow rate:	1.5 mL/min
Injection volume:	10 µL
Detector:	UV set at 238 nm
Retention time: Fluroxypyr-meptyl Internal standard	 approximately 45.4 minutes approximately 21.0 minutes

PREPARATION OF INTERNAL STANDARD SOLUTION
Prepare sufficient internal standard solution to provide 10.0 mL for every standard and sample to be analysed. For one liter, accurately weigh about 3g of diethyl phthalate into a glass weighing boat or small glass beaker. Transfer to a 1 L volumetric flask with methanol and make up to volume with the same solvent, shake thoroughly to mix.

PREPARATION OF STANDARD SOLUTIONS
It is recommended that at least two standard solutions are prepared. For these, weigh accurately, into separate 100 ml volumetric flasks, about 0.04g and 0.06g of Fluroxypyr-meptyl analytical standard. Add, by pipette or from a suitable dispenser, 10.0 mL internal standard solution. Make up to volume with methanol. Stopper and mix thoroughly by inversion and, if necessary, immerse in an ultrasonic bath to dissolve all solids. Inject aliquots of the prepared standard mixtures onto the HPLC under the conditions given above.

SAMPLE ANALYSIS

It is recommended that samples are analysed at least in duplicate. The required weight of sample should be calculated so that the amount of Fluroxypyr-meptyl in that weight falls between the amounts present in the two standard solutions.

Add to each flask a 10.0 mL aliquot of internal standard solution (using the same pipette or suitable dispenser as employed for the standards) and make up to volume with methanol. Place the flasks in an ultrasonic bath until any solids have fully dissolved to ensure that the Fluroxypyr-meptyl is completely dissolved. Shake thoroughly by hand to ensure homogeneity.

Inject aliquots onto the HPLC, under the same conditions as for the standards, bracketing each two or three sample injections between the two different standard mix injections, e.g., a sequence such as Std. 1, Sample 1(a), Sample 2(a), Std.2, Sample 1(b), Sample 2(b), Std.1, etc. etc.

CALCULATIONS

From the areas of the peaks produced, calculate the Relative Response Factor (F) for Fluroxypyr-meptyl as follows:

$$F = \frac{\text{Area Fluroxypyr-Meptyl Peak}}{\text{Area Int. Std. Peak}} \times \frac{\text{Wt. Int. Std. in 10.0 ml}}{\text{Wt.'Pure' Fluroxypyr-Meptyl}}$$

where :

$$\text{weight of 'pure' Fluroxypyr-Meptyl} = \frac{\text{Wt. Std. Fluroxypyr-Meptyl taken x \% Purity}}{100}$$

The amount of Fluroxypyr-meptyl in the samples is calculated from:

$$\text{\% w/w Fluroxypyr-Meptyl} = \frac{\text{Area Fluroxypyr-Meptyl Peak}}{\text{Area Int. Std. Peak}} \times \frac{\text{Wt. Int. Std. in 10.0 ml}}{\text{Wt. Sample taken}} \times \frac{100}{F(Av)}$$

where :

F(Av) represents the average Response Factor, for Fluroxypyr-Meptyl, obtained from the standard solutions injected immediately before and after any particular group of sample injections.

The method was validated for accuracy, linearity and precision.

DP BARCODE: D373465; **FILE SYMBOL No.:** 35935-53; **PRODUCT:** Fluroxypyr Technical

CONFIDENTIAL APPENDIX

Proposed alternate CSF (dated 11-20-09)

[redacted]

Pages 8-14*Manufacturing process information may be entitled to confidential treatment*